

REMARKS/ARGUMENTS

1. *Status of the claims*

Claims 1, 3, 20, 22, 25-27 and 29 are amended and claims 35-37 are added. Claims 1, 3, 5-16, 19, 21-23, 25-29, 33-37 are pending and under consideration with entry of this Amendment.

2. *Support for the Amendments*

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted. For example, the amendment to claim 1 is supported on, e.g., page 52, lines 3-5 of the specification. No new matter is introduced by the Amendment.

3. *Claim Objections*

Claim 21 was objected to as depending from a canceled claim (claim 20). Applicants respectfully note that claim 20 is not canceled. However, claim 20 depends from claim 17, which is canceled. Claim 20 is amended herein to depend from claim 1, thereby rendering the objection moot.

Claims 25, 26 and 27 were objected to as dependent from a subsequent claim. As amended, claims 25-27 depend from claim 22, thereby rendering the rejection moot.

4. *Rejections under 35 U.S.C. § 112, second paragraph*

A. *Claims 1 and 22*

Claims 1 and 22 were rejected as allegedly vague for the recitation "other Bacillus." As amended, the claims recite "from non-anthraxis *Bacillus* species." The scope of the claim is not changed by the amendment. The claims indicate that the antibody does not form a complex with species other than *B. anthracis*. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. Claim 3

Claim 3 was rejected as allegedly indefinite for reciting "strain." As amended, the claim recites "the *B. anthracis* present in the test sample is encapsulated." The scope of the claim is not changed by the amendment. Applicants respectfully request withdrawal of the rejection.

C. Claim 29

Claim 29 was rejected as allegedly indefinite. The rejected claim recites "the kit further comprises a positive control that comprises a polypeptide that comprises an antigenic determinant of a *B. anthracis* surface array protein." Thus, the kit contains a polypeptide comprising an antigenic determinant of the surface array protein. The antigenic determinant would act as a positive control to which the anti-SAP antibodies of the kit would bind. The skilled artisan would understand that an antigenic portion of the SAP could be used as a positive control. For example, a fusion protein comprising a fragment of the SAP protein could be used. To further clarify the invention, applicants have added the phrase "wherein the antigenic determinant binds to said first antibody." Accordingly, Applicants respectfully request withdrawal of the rejection.

5. Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 5-16, 19, 21-23, 25-29 and 33-34 were rejected as allegedly not described in the specification so as to enable those of skill in the art to make and use the invention. The Examiner appears to argue that performing the methods of the invention require undue experimentation. The allegation is based on several alleged difficulties that one of ordinary skill in the art might face in practicing the invention:

1) that the surface array protein might not be present in all *B. anthracis* strains and therefore that the claimed method or kit might not detect any and all *B. anthracis* strains;

2) that spores might not express the surface array protein;

- 3) that two epitopes might not be available on the surface array protein for two antibodies to bind; and
- 4) that unspecified environmental “contaminants” might interfere with the method under certain conditions. *See*, Paper No. 16, page 5.

Applicants respectfully traverse the rejection. Applicants respectfully submit that no *prima facie* case of a lack of enablement has been established by the Examiner. In addition, Applicants provide herewith a declaration of Dr. Gunars Valkirs, describing why one of ordinary skill in the art would readily acknowledge that the instant specification satisfies the enablement requirement. Moreover, data gathered by the Centers for Disease Control and Prevention, United States Department of Health and Human Services, are provided demonstrating that the instant specification is enabling for the full scope of the present claims.

A. The Examiner Has Not Presented A Prima Facie Enablement Rejection

The standard for determining enablement is whether the specification as filed provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

A patent specification is presumptively enabling, and the Examiner bears the initial burden of advancing reasoning and evidence establishing a *prima facie* case that one of skill in the art would find the specification inconsistent with enablement. *See*, MPEP § 2164.04 (“it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure”).

The Examiner has based the rejection on a broad allegation that the specification is somehow speculative, coupled with a recitation of various difficulties that may be encountered in practice. This, however, is not sufficient to establish a *prima facie* case of a lack of enablement. *See, e.g., Ex parte Miyada*, page 5 (Bd. Pat. App. Int. 1997). It has long been established that a broad allegation that a disclosure is speculative, coupled with a recitation of various difficulties that might be encountered in practice, is not a sufficient basis to question a presumptively enabled disclosure. *See, e.g., Ex parte Miyada*, page 5 (Bd. Pat. App. Int. 1997) (citing *In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956)). Likewise, to the extent the Examiner is asserting that the claims may include certain inoperative embodiments, or may not accomplish each and every objective recited in the specification, these considerations are also insufficient to establish a *prima facie* case of a lack of enablement. *See, e.g., Ex parte Tom-Moy*, page 6 (Bd. Pat. App. Int. 1996) ("it is not a function of the claims to specifically exclude possible inoperative combinations," citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)); *Ex parte Barnett*, page 6 (Bd. Pat. App. Int. 1996) ("a claimed invention need not accomplish all objectives stated in the specification," citing *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958 (Fed. Cir. 1983), *cert. denied* 469 U.S. 835 (1984)).

Indeed, one could always propose conditions where the surface array protein of a particular *B. anthracis* strain might not be detectable (*e.g.*, in the presence of 8 M urea, where antibody binding typically does not occur, or where the strain has been engineered to delete the surface array protein entirely). But the speculative possibility that a *B. anthracis* strain might exist that would not be detected, or that under certain circumstances a contaminant might prevent detection, or even that spores would not be detected, does not provide any evidence that a method for detecting *B. anthracis* surface array protein may not be practiced in accordance with the claims. Accordingly, the Examiner has stated any reason to believe that the invention does not work as claimed and therefore has not set forth a *prima facie* enablement rejection.

B. Data Provided In The Working Examples And Declaration Demonstrate That The Claims Are Enabled For Their Full Scope

The application, declaration and data from the CDC provided herein rebut each of the allegations made by the Examiner.

i. All evidence indicates that the surface array protein is present in all B. anthracis strains

The Examiner asserted that:

[i]t is not clear whether or not all spores will express SAP (SEQ ID NO:1) and the claims method or kit would be able to detect SAP (SEQ ID NO:1) in any and all B anthracis strains in a test sample.

See, Paper No. 16, page 5.

The Examiner appears to raise this issue in part because the examples describe experiments with the Sterne strain, which is a laboratory strain.

First, as explained in paragraph 11 of the declaration of Dr. Valkirs, antibodies directed to the *B. anthracis* surface array protein set forth in SEQ ID NO: 1 react with **vegetative cells** and with surface array protein present in culture **supernatants** obtained from *B. anthracis* cultures that include spores. Antibodies directed to the *B. anthracis* surface array protein set forth in SEQ ID NO: 1 do **not** react with *B. anthracis* spores.

Second, the Examiner does not provide any evidence or reasoning why the skilled artisan would not extrapolate the exemplary methods for specifically detecting the surface array protein of the *B. anthracis* Sterne strain to other *B. anthracis* strains. As discussed by Dr. Vakirs in the declaration submitted herewith, the Sterne strain is commonly used by those of skill in the art in order to avoid the use of dangerous pathogenic anthrax bacteria in a laboratory environment, and is widely accepted by those of skill in the art as a surrogate for virulent *B. anthracis* strains (whether in the environment or otherwise). See, e.g., Valkirs declaration, paragraph 7. Accordingly, it is scientifically sound to assume that the Sterne strain is representative of non-laboratory strains.

Furthermore, as evidence that the methods described in detail in the instant specification can, in fact, be extrapolated to other *B. anthracis* strains, Applicants have obtained by Freedom of Information Act request a certified government document from the Centers for

Disease Control and Prevention, United States Department of Health and Human Services (the "CDC"). As described in paragraph 5 of the Valkirs declaration, the CDC purchases from the Applicant two antibodies described in the instant specification, and uses these antibodies "in a CDC-developed Time-Resolved Fluorescence Assay Specific for *B. anthracis* Cells" (quote from CDC document). The CDC and 125 laboratories in its affiliated network have demonstrated that these antibodies detect surface array protein from a wide variety of *B. anthracis* strains, including human and animal isolates. Thus, the claimed methods are effective in detecting both laboratory- and environmentally-derived *B. anthracis*. It is particularly notable that **all** *B. anthracis* strains tested were detected by the CDC, while no non-*anthracis* strains cross-reacted.

The application and declaration therefore prove that the claimed methods are useful for detecting a wide range of *B. anthracis* strains. Considering this data, Dr. Vakirs concludes that the skilled artisan could practice the claimed detection methods and provide the claimed kits using readily available starting materials, and methods that were well known in the art and the '947 application as a guide. The Declaration and CDC data prove that that the surface array protein is present and detected in all *B. anthracis* strains tested and provides no reason to believe that other *B. anthracis* strains would not react similarly.

C. Those Of Skill In The Art Would Recognize That Multiple Epitopes On The Surface Array Protein Can Be Detected

The Examiner also argued that "the specification fails to teach antibodies that bind to different epitopes" and that "it is unclear which epitopes the two antibodies bind." See, Paper No. 16, page 5.

As an initial matter, Applicants note that the Examiner has not set forth any reason why it is necessary to provide detailed information regarding which epitope is bound. As discussed below, the evidence present in the application demonstrates that a number of epitopes appear to be useful for specific detection of *B. anthracis*. The Examiner has not cited a single counterexample where a specific epitope of surface array protein was required to detect *B. anthracis*.

Furthermore, as discussed in the Declaration of Dr. Valkirs, the examples in the present application state that a recombinant polyclonal antibody (IIT005.1.C.11.1) was used to specifically detect surface array protein in *B. anthracis*. A polyclonal antibody preparation is a preparation comprised of different antibodies, each of which binds to the same protein, but not necessarily the same epitope. As explained in the Declaration of Dr. Valkirs, the skilled artisan would expect that a polyclonal antibody preparation, such as that described in the present application, would bind to multiple epitopes on the surface array protein. *See*, Declaration of Dr. Gunars Valkirs, paragraph 10.

The Declaration of Dr. Valkirs states that given the size of the surface array protein compared to the size of an average epitope recognized by an antibody (785 amino acids, compared to an average epitope size of about 15-20 amino acids), the skilled artisan would not seriously question whether two antibodies could be obtained that bind to different epitopes on the surface array protein. Thus, at most routine experimentation would be required to obtain antibodies that bind different epitopes.

Moreover, Example 7 beginning on page 50 of the specification explicitly teaches sandwich immunoassays using appropriate antibody pairs. As noted above, one of these pairs (shown in Table 2) represents the antibodies purchased by the Centers for Disease Control and Prevention from Biosite, Inc. for the detection of *Bacillus anthracis*. Regardless of whether the present application explicitly discloses which epitopes of the surface array protein any particular antibody binds to, the skilled artisan would readily acknowledge that appropriate antibody pairs could be readily prepared and identified based on the teaching in the specification.

D. There Is No Evidence That Environmental "Contaminants" Interfere With The Claimed Methods

The Examiner also argued that that unspecified environmental "contaminants" might interfere with the claimed method under certain conditions. *See*, Paper No. 16, page 5. Absent any evidence from the Examiner that contaminants would be expected to interfere with detection, the Examiner has not met her burden of proof. Indeed, there are numerous antibody-based assays used to detect molecules in the environment. Does the Examiner believe that it is

generally impossible to detect organisms in the environment using antibodies or is there some specific aspect of the currently claimed methods that makes the Examiner question whether interference from contamination may occur? The Examiner has not provided any evidence to suggest why either option would be a problem requiring undue experimentation.

Finally, it is unclear how "contaminants" would interfere with detection. As described herein, the closest relatives of *B. anthracis*, i.e., other *Bacillus* species, do not react with anti-*B. anthracis* surface array protein antibodies. Therefore, there is no reason to believe that other less related contaminants would interfere with detection of *B. anthracis*.

E. Summary

The Examiner has not set forth a *prima facie* enablement rejection because she has not provided any reasonable basis to believe that the invention does not work as claimed. Moreover, the Declaration of Dr. Valkirs and evidence from the CDC demonstrate that the methods and kits of the invention are useful for detecting any *B. anthracis* strain but is not reactive with other *Bacillus* species. Therefore, Applicants respectfully request withdrawal of the rejection.

6. *Rejection under 35 U.S.C. § 102(b)*

Claims 22, 25, 29, 33 and 34 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Phillips *et al.*, *J. Appl. Bacteriol.* 64:47-55 (1988). In addition, the Examiner rejected claims 22, 23, 26, 27, 33 and 34 as allegedly anticipated by Phillips *et al.*, *FEMS Microbiol.* 47:169-178 (1988). According to the Examiner, the antibodies disclosed in the cited references inherently anticipate the claims. Applicants respectfully traverse the rejection.

A. The Examiner Has Not Presented A Prima Facie Anticipation Rejection

Applicants respectfully submit that no *prima facie* case of anticipation has been established by the Examiner. Instead, the Examiner has attempted to improperly shift the burden to Applicants to prove that the cited publications do not anticipate the claims. In order to

anticipate a claim, a single prior art reference must provide each and every element set forth in the claim.

The Examiner's rejection is not based upon an explicit disclosure of a device meeting each and every element of the claims. Rather, the rejections are based on the alleged inherent disclosure by the cited publications of antibodies that specifically bind to the *B. anthracis* surface array protein set forth in SEQ ID NO: 1. *See, e.g.*, Paper No. 16, page 7, first paragraph and last full paragraph.

In arguing that an element set forth in the claims is inherent in a cited publication, the Examiner bears the burden of establishing by extrinsic evidence that the "missing descriptive matter is necessarily present in the thing described in the reference." MPEP §2112, emphasis added; *see also, Ex parte Lim*, 2002 WL 519786 (Bd. Pat. App. And Interf.) ("It is well settled that the examiner has the burden of making out a *prima facie* case of anticipation... either expressly or under the principles of inherency"). The fact that a certain result or characteristic may occur is not sufficient to establish the inherency of that characteristic. *See, e.g., In re Robertson*, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient").

The Examiner provides no reasoning or evidence in support of the alleged inherency. Instead the Examiner simply asserts that it is so. Applicants respectfully submit that such a statement does not meet the Examiner's initial burden of establishing by extrinsic evidence that the missing descriptive matter is necessarily present in the reference.

Moreover, the prior art teaches that antibodies raised against **spores** do not react with surface array protein (*see, e.g.*, specification, page 3, lines 13-15). Since the antibodies described in the Phillips *et al.* references are raised against anthrax **spores**, there is no reasonable basis to believe they inherently bind *B. anthracis* surface array protein.

Furthermore, the Examiner inappropriately attempts to extend the flawed rejection by asserting that the burden is placed upon the applicant to show a novel or unobvious difference between the claims and the cited publications. Paper No. 16, page 8. Applicants respectfully submit, however, that the Examiner has no basis to shift this burden to Applicants. The

conditions under which the burden may be shifted to applicants to prove no anticipation is described in *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977):

Where... the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily possess the characteristics of his claimed product.

In the present case, the claimed and prior art methods are similar only in that each relies on an antibody that recognizes some *B. anthracis* protein(s). But, as discussed above, the antigens used to raise the antibodies differed substantially between the present invention and the cited publications. Thus, the Examiner has not shown that either the products or the methods used to produce the products are identical or substantially identical, and so the burden remains on the Examiner to support the flawed anticipation rejection.

B The Antibodies Described In The Cited Reference Have A Different Reactivity Than Those Claimed

Although Applicants respectfully submit that the burden to establish a *prima facie* case of anticipation remains on the Examiner in the present case, the Valkirs declaration submitted herewith is offered to explain why the skilled artisan would readily acknowledge that the cited publications do not inherently disclose the instantly claimed invention. As explained in paragraph 11 of the declaration, antibodies directed to the *B. anthracis* surface array protein set forth in SEQ ID NO: 1 reacts with vegetative cells and with surface array protein present in culture supernatants obtained from *B. anthracis* culture. Antibodies directed to the *B. anthracis* surface array protein set forth in SEQ ID NO: 1 do not react with *B. anthracis* spores.

In contrast, as explained in paragraphs 12-15 of the Valkirs declaration, the antibodies disclosed in the cited publications are raised against spore preparations, and either do not recognize vegetative cells at all, or recognize both vegetative cells and spores. Thus, none of the cited antibodies have the reactivity demonstrated for the antibodies of the invention.

The Phillips *et al.* *FEMS Microbiol. Immunol.* 1988 publication cited by the Examiner discloses three antibody preparations: a monoclonal raised against intact spores (denominated "E12"), a monoclonal raised against SDS-extracted spores (denominated "A9"),

and “hyperimmune mouse serum” raised against spores. The publication states that neither the E12 nor the A9 antibodies react with *B. anthracis* vegetative cells. *See, e.g.*, page 175, left column, last paragraph. In contrast, SAP is found in vegetative cells, and the SAP-specific antibodies as recited in the claims bind to vegetative cells. Therefore, since the cited antibodies do not bind to vegetative cells, whereas the claimed antibodies do, the antibodies described in the Phillips *et al.* reference cannot describe antibodies that specifically bind to a *Bacillus anthracis* surface array protein as displayed in SEQ ID NO:1.

As for the hyperimmune mouse serum disclosed in the Phillips *et al. FEMS Microbiol. Immunol.* 1988 publication, this serum was raised against whole spores (*see, e.g.*, page 171, right column, second full paragraph), and recognized both whole spores and vegetative cells (*see, e.g.*, Tables 3, 4, and 5). As discussed above, *B. anthracis* surface array protein is not available to antibodies on whole spores. Therefore whole spores should not raise antibodies that bind to surface array protein. Indeed, the antibodies that specifically bind to the *B. anthracis* surface array protein referred to in the present claims do not bind to whole spores (*see, e.g.*, CDC data; and the present specification, page 49, lines 26-28, which indicates that antisera to spore coat proteins is used as a negative control).

Similarly, the Phillips *et al. J. Appl. Bacteriol.* 1988 publication cited by the Examiner discloses hyperimmune mouse serum raised against whole formaldehyde-treated spores (*see, e.g.*, page 49, left column, first full paragraph). Formaldehyde treatment would cross-link the surface array protein within the spore and would not extract surface array protein from within whole spores. Thus, formaldehyde-treated spores would not be expected to provide surface array protein as an antigen.

Furthermore, only certain hyperimmune mouse serum recognized vegetative cells (*see, e.g.*, page 51, first full paragraph), and this hyperimmune mouse serum also recognized whole spores (*see, e.g.*, Table 2). Again, because the antibodies that specifically bind to the *B. anthracis* surface array protein referred to in the present claims do not bind to whole spores, the skilled artisan would conclude that the hyperimmune mouse serum disclosed in this publication is substantially different from the antibodies referred to in the claims, and does not specifically bind to *B. anthracis* surface array protein as required by the present claims.

In view of this data Dr. Valkirs concludes in his declaration that the skilled artisan would believe that the antibodies disclosed in the cited publications do not specifically bind to the *B. anthracis* surface array protein set forth in SEQ ID NO: 1, as required by the present claims. For this reason, the cited publications do not anticipate the instant claims.

C. Summary

Because the Examiner has not met the burden required to establish inherency of the claimed invention, and because the cited publications do not disclose each and every element of the claimed invention, no *prima facie* case of anticipation has been established. Accordingly, Appellant respectfully requests that the rejection under 35 U.S.C. §102 be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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